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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	6

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/238,741	Braslawsky et al
Examiner	**Group Art Unit**
Larry R. Helms Ph.D.	1642

X Responsive to communication(s) filed on *11 Sep 2000*

This action is **FINAL.**

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

X Claim(s) *1-46* is/are pending in the applicat

Of the above claim(s) *3, 10-13, 15-23, 30-33, 38-40, and 42-44* is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *1, 2, 4-9, 14, 24-29, 34-37, 41, 45, and 46* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

X The specification is objected to by the Examiner.

X The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s).

Interview Summary, PTO-413

SEE OFFICE ACTION ON THE FOLLOWING PAGES

DETAILED ACTION

1. Applicant's election of Group II, claims 1-2, 5-9, 14, 24-29, 37, 41, 45, and 46 in part drawn to an antibody heterodimer, and claims 4 and 34-36 in Paper No. 4 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-2, 5-9, 14, 24-29, 37, 41, 45, and 46 drawn to antibody homodimers and claims 3, 10-13, 15-23, 30-33, 38-40, 42-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected. Election was made **without** traverse in Paper No.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). The name of the inventor Michael V. LaBarre has been altered to replace the

Appropriate correction is required.

Specification

5. The disclosure is objected to because of the following informalities:

a. The application on page 22, line 10-11 contains a U.S. Patent application , 08/819,866, which is now U. S. Patent 5,830,698. The application should be updated to indicate the current status of all pending U. S. applications.

Appropriate correction is required.

Claim Objections

6. Claims 1-2, 5-9, 14, 24-29, 37, 41, 45, and 46 are objected to because of the following informalities:

a. Claims 1-2, 5-9, 14, 24-29, 37, 41, 45, and 46 are drawn to a non-elected invention.

b. Claim 28 and 41 are dependent on non-elected claim 23.

Appropriate correction is required.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-2, 4, 5-9, 24-29, 34, 36, 37, 45 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-2, 4, 5-9, 24-29, 34, 36, 37, 45 and 46 are indefinite for reciting incomplete method claims in claims 1, 24, 37, and 45 which does not include a resolution step which reads back on the preamble of the claimed method. The claims should conclude with a step of producing an antibody dimer, for example, as required by the preamble, which recites "a method for producing an antibody dimer".

b. Claims 1-2, 4, 5-9, 24-29, 34, 36, 37 are indefinite for reciting "desired binding specificity" and "desired specificity" in claims 1, 24, and 37 because the exact meaning of the phrase is not clear. Does the phrase mean that the binding specificity is hoped for? In addition, it is unclear who or what determines the "desired binding specificity".

c. Claims 1-2, 4, 5-9, 24-29, 34, 36, 37 are indefinite for reciting "introducing at least one cysteine codon" in claims 1, 24, and 37 because the exact meaning of the phrase is not clear. Does the phrase mean that every residue in the heavy chain can be substituted for a cysteine or an undisclosed number of cysteine residues added to the heavy chain?

intra or inter molecular disulfide bonds of said antibody molecule" in claims 1, 24, and 37

because the exact meaning of the phrase is not clear. What inter or intra molecular disulfide bonds are reduced?

e. Claims 1-2, 4, 5-9, 24-29, 34, 36, 37 are indefinite for reciting "thereby enhance the function of antibody dimers" in claims 1, 24, and 37 because the exact meaning of the phrase is not clear. What function is being enhanced?

f. Claims 1-2, 4, 5-9, 24-29, 34, 36, 37 are indefinite for reciting "allowing sufficient time" in claims 1 and 24 because the exact meaning of the phrase is not clear. It is unclear what determines "sufficient time" because the claims do not state that the dimerization reaction must be completed.

g. Regarding claims 1, 24, and 37 the phrase "optionally terminating" renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

h. Claim 36 is indefinite in the recitation of "C2B8/p5E8" because other laboratories inventors may use the same laboratory designation to refer to different antibodies. Amendment of the claim to insert the corresponding ATCC accession number of the hybridoma which produces the antibody(s) or to add the SEQ ID Nos of the heavy and light chain variable regions would overcome this rejection.

i. Claims [illegible]

the light chain have the same "desired specificity" as the heavy chain recited in the claims?

j. Claims 1, 24-27, 29, 37, are indefinite for reciting "antibody dimer" in claims 1, 24, and 37 because the exact meaning of the phrase is not clear. Does the phrase mean an entire IgG antibody dimer or a light chain and a heavy chain?

k. Claim 9 is indefinite for reciting "the method of claim 2" because there is no method in claim 2.

l. Claim 5 is indefinite for reciting "capable of activating components of the complement system" because the exact meaning of the phrase is not clear. What components are being claimed and how is the complement system activated and what cells are involve?. In addition, with respect to "capable", does the dimer activate the complement system or not?

m. Claim 9 is indefinite for reciting "capable of initiating programed cell death (apoptosis)" because the exact meaning of the phrase is not clear. Does the dimer initiate apoptosis or not and it is unclear what is encompassed such as what cells and how cell death is achieved.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[redacted] antibody heterodimer with antibodies which specifically bind CD20 and CD23(p5F8) comprising

obtaining or constructing a DNA molecule that encodes an antibody that binds antigen and comprises a heavy chain and a light chain with the same antigen binding specificity, wherein the heavy chain has a cysteine residue introduced at position 444 (Kabat numbering) that does not interfere with antigen binding or proper folding and compositions comprising such and wherein the anti-CD20/anti-CD23 dimer antibody activates apoptosis in CD20+ B cell lymphomas, does not reasonably provide enablement for a method for producing any IgG antibody heterodimer wherein the antibody does not bind antigen, comprises a light chain from any antibody paired with any heavy chain wherein the heavy chain contains a cysteine residue introduced anywhere even in the CDRs and pharmaceutical compositions comprising such and wherein the antibody heterodimer initiates apoptosis or complement mediated cell killing in any cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of

wherein the antibody does not bind antigen or does not comprise an entire antibody comprising a

heavy chain and a paired light chain that binds antigen and a hinge region and a Fc region, comprises a light chain from any antibody paired with any heavy chain wherein the heavy chain contains a cysteine residue introduced anywhere, even in the CDRs and pharmaceutical compositions comprising such.

The specification teaches a heterodimer of anti-CD20 and anti-CD23 (see Example 4) and the binding of the heterodimer to CD20 and CD23 antigens (see Example 5b). The specification fails to enable an antibody heavy chain of CD20 or CD23 with any light chain or introducing a cysteine anywhere in the heavy chain other than at position 444 (numbering of Kabat).

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light

CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc

Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the claims which may contain light and heavy chains that are not from the same antibody have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional antibody can be obtained by replacing residues in the CDRs. Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

Claim 41 is drawn to a pharmaceutical composition comprising the antibody of claim 28. Enablement of a "pharmaceutical composition" is considered to rest on a teaching of in vivo administration for purposes consistent with the intended use disclosed in the specification. The disclosed intended use for the claimed pharmaceutical compositions is for the treatment of cancer and autoimmune disorders (see page 20). Thus, the nature of the invention is a therapeutic

formulating compositions in pharmaceutically acceptable carriers, there is insufficient guidance

which would enable one skilled in the art to use the claimed compositions for their intended purpose, viz., for the treatment of cancer and autoimmune disorders.

At the time the invention was made, pharmaceutical compositions comprising the claimed antibodies were not routinely used for the treatment of cancer and autoimmune disorders. The specification lacks guidance by way of general methods or working examples which teach an amount of the polypeptide which would be used for this purpose. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art, such as treatment of cancer and autoimmune disorders. Accordingly, there is no objective basis upon which the skilled artisan would reasonably be able to determine or predict an amount of the claimed composition effective for its intended use.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to use the claimed invention.

11. Claim 35 is rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the

a. It is unclear if a cell line which produces the antibodies having the exact chemical identity of C2B8 and p5E8 are known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

b. For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species C2B8 and p5E8. Deposit of the hybridoma would satisfy the

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 2, 4, 28, 41, and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Brenner et al (Science 229:81-83, 1985).

a. The claims recite an IgG/IgG heterodimer produced by a method and compositions comprising such.

b. Brennan et al teach a bispecific heterodimeric antibody. The method in which the IgG/IgG heterodimer were produced is immaterial to their patentability. "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product I in the product-by-process claim I is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re* Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985). See also MPEP 2113.

Claim Rejections - 35 USC § 103

obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-2, 4-9, 14, 24-29, 34-37, 41, and 45-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caron et al (J. Exp. Med. 176:1191-1195, 1992) and further in view of

et al [b] (Blood 83:435-445, 1994).

a. The claims recite a method for producing an antibody IgG/IgG heterodimer comprising obtaining or constructing a DNA molecule that encodes a heavy chain and introducing at least one cysteine codon and expressing the DNA with DNA encoding a light chain and purifying the antibody and contacting the antibody with a reducing agent to reduce the intra or inter molecular disulfide bonds and either allowing for dimerization or prior to this step adding a thiol reactive group, which is maleimido and dithiopyridal group, introduced on another antibody which does not have a cysteine group introduced . Further claimed is an IgG/IgG heterodimer, which is capable of activating components of the complement system and which kills cells and binds Fcgamma on effector cells and on immune cells and is capable of initiating apoptosis wherein the dimer is reactive against CD20 and CD23 and wherein the IgG's are of the same or different subclass and different isotypes and bind two different epitopes and is C2B8/p5E8 and a method wherein a cysteine molecule placed which inhibits formation of an intramolecular disulfide bridge between sister heavy chains on the same antibody and compositions comprising such.

b. Caron et al teach a method for producing a dimeric IgG which comprises converting by recombinant DNA mutagenesis the serine at position 444 in the heavy chain to a cysteine. The method comprises purifying the antibody and reacting with Ellman's reagent and allowing dimerization. (See Materials and methods). The antibody has enhanced CMC and ADCC with

CD20 antibody. These deficiencies are made up in the teachings of Fanger et al, Cumber et al, and Reff et al [a] and [b].

c. Fanger et al teach bispecific antibodies by chemical cross linking or by molecular genetic approaches (see page 102, section II and Figure 1).

d. Cumber et al teach a bispecific antibody produced by chemical cross linking with a maleimido group with the cysteine residues (see Figure 2) wherein one is introduced in the heavy chain (see page 22, Results).

e. Reff et al [a] teach the anti-CD23 antibody (p5E8) and Reff et al [b] teach the anti-CD20 antibody (C2B8).

f. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the method of Caron et al and/or add a thiol cross linking agent as taught by Cumber et al and produce a bispecific antibody as taught by Fanger et al with the anti-CD21 and anti-CD23 antibodies as taught by Reff et al [a] and [b].

g. One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in using the method of Caron et al and/or add a thiol cross linking agent as taught by Cumber et al and produce a bispecific antibody as taught by Fanger et al with the anti-CD21 and anti-CD23 antibodies as taught by Reff et al [a] and [b] because Caron et al teach

"[illegible]

and "multimeric constructs of IgG may have advantages relative to those forms that are found

naturally." (See abstract). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in using the method of Caron et al and/or add a thiol cross linking agent as taught by Cumber et al and produce a bispecific antibody as taught by Fanger et al with the anti-CD21 and anti-CD23 antibodies as taught by Reff et al [a] and [b] because Fanger et al teach "Chemical linkage is the most straightforward procedure for making a pure BsAb;" (see page 102) and "BsAb can bind both to target cells (pathogens and tumors) and to toxins, enzymes, or triggering molecules on leukocytes such as T-cell receptors (TcR) or FcγR." (See page 102). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in using the method of Caron et al and/or add a thiol cross linking agent as taught by Cumber et al and produce a bispecific antibody as taught by Fanger et al with the anti-CD21 and anti-CD23 antibodies as taught by Reff et al [a] and [b] because Cumber et al teach that "the sulfydryl group so introduced served as a specific site for the attachment of the homobifunctional cross-linking reagent" (see page 122). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in using the method of Caron et al and or add a thiol cross linking agent as taught by Cumber et al and produce a bispecific antibody as taught by Fanger et al with the anti-CD21 and anti-CD23 antibodies as taught by Reff et al [a] and [b] because Reff et al [a] teach "CD23,

antibody are effective in treating any disease wherein inhibition of IgE production is

therapeutically desirable" (column 38, lines 42-46) and Reff et al [b] teach CD20 is on the surface of B-cell lymphomas and C2B8 showed ability to bind to human C1q, mediate complement-dependent cell lysis of human B-lymphoid cells. In addition, one skilled in the art would want to produce a heterodimeric anti-CD20 and CD23 antibody because one skilled in the art would know that targeting the CD23 would result in lower levels of I.e. and targeting the CD20 with C2B8 would result in the lysis of the B-cell. In addition, it would be obvious to place a cysteine residue in a heavy chain at a position that does not form an intramolecular disulfide bridge between sister heavy chains on the same antibody.

h. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusions

17. No Claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D. whose telephone number is (703) 306-5879. The

examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a

general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

Sheila Huff

SHEELA HUFF
PRIMARY EXAMINER